REMARKS

The Applicants wish to thank Examiner Padmanabhan for informing Applicants' representative that Examiner Chong has been substituted for Examiner Sharareh in examining the present application.

Claims 1-10 and 12-20 are currently pending and Claims 1-10 and 12-20 have been rejected by the Examiner. Applicants submits that Claims 1, 9 and 17 have been amended. Support for the amendment is found in the specification on page 4, lines 3-11 and page 20, lines 18-27.

The presently amended claims are drawn to a microbubble for the in vivo transport of physiological gases wherein the microbubble comprises a membrane entrapping at least one fluorocarbon gas and at least one modifier gas, wherein the ratio of the modifier gas to the fluorocarbon gas is from about 1:100 to about 1000:1, wherein the partial pressure of the resulting gas mixture at 37° C is greater than the equilibrium partial pressure of the fluorocarbon gas, and wherein the microbubble grows and shrinks to maintain osmotic equilibrium with the physiological gas saturation of the surrounding external medium.

Rejection under obviousness double patenting

Claims 1-10, and 12-20 have been rejected under the judicially created doctrine of obviousness-type double patenting over the claims of U.S. Patents 6,372,195; 6,258,339; 5,695,741; 5,639,443; 5,798,091; 5,804,162 and 6,193,952. Applicants wish to thank the Examiner for holding this rejection in abeyance until allowable subject matter has been declared.

Rejection under 35 U.S.C. §103(a)

Claims 1-10, 13-18, and 20 have been rejected under 35 U.S.C. §103(a) over U.S. Patent 5,413,774 (Schneider). Applicants respectfully traverse.

The Examiner maintains that Schneider meets the structural and functional limitations of the present invention. Furthermore, the Examiner asserts that Schneider only fails to "specifically recite the instantly claimed ranges of modifier gas to fluorocarbon gas" and a skilled artisan will "optimize the concentrations of individual gases" in Schneider's microbubbles by "routine experimentation to observe the most effective clinical results". Applicants respectfully disagree. The predecessor to the Federal Circuit has held as follows:

> A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of optimum or workable ranges of said variable might be characterized as routine experimentation". *See MPEP §2144.05; In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977).*

Thus, to be recognized as a result-effective variable, i.e. a variable which achieves a recognized result, Schneider must teach a parameter which requires optimization to arrive at the claimed ranges. Applicants note that Schneider does not teach any such parameter. The parameter taught by Schneider is based on the solubility of a selected gas in water at 25°C and its molecular weight. This gas which fits the parameter as shown below is selected to replace air in microvesicles and is given by the following requirement:

Solubility of gas in water /√(Molecular weight of gas) ≤ Solubility of air in water/√ (Molecular weight of air).

Simplifying the above expression Schneider arrives at the following parameter:

Solubility of gas in water /√ (Molecular weight of gas) ≤ 0.0031.

According to Schneider gases that fit the above criteria are suitable for replacement of air in microbubbles. See Schneider at col. 3 and col. 4. By contrast, applicants have found out that some of the fluorocarbon compounds, such as $CHClF_2$, which are gas osmotic agents in the present invention, do not fit this criteria. See specification page 20, lines 28-30. Thus, solubility of a selected gas is not a sufficient parameter to make it a result-effective variable. Furthermore, fluorocarbon compounds such as Freon-F-21 (Dichloromonofluoromethane) also do not fit the criteria. See Table below:

Table:

Compound		MW	Sgas	Sgas/√MW
$CHClF_2$	Chlorodifluoromethane Freon-22	86	0.78(a)	0.084
$CHCl_2F$	Dichloromonofluoromethane Freon-F-21	102.92	2.066(b)	0.204

(a) See Schneider Table 6a, last line

(b) See Gas Data Sheet (Attached herewith for Examiner's reference)

Schneider merely states that a gas fitting the solubility criteria can replace air without any mention on the ratios of gases and maintains that complete replacement of the gases within the microbubble by the fluorocarbon gas is preferred. See Schneider at col. 5 lines 16-18. Schneider's criteria is not a result-effective variable in terms of identifying the gases, let alone optimizing the range. Accordingly Schneider's criteria ***teaches away*** from the present invention.

Applicants further note that criteria set forth above is applicable mainly to gases and does not account for the fluorocarbon and perfluorocarbon osmotic agents of the present invention. Schneider in his criteria considers water solubility of gases at 25°C/1-atm pressure. By contrast, Applicants microbubbles contain modifier gases such as air and gas osmotic agents which

include gases and the vapors of liquids that have vapor pressures greater than 75 mm Hg at 37°C. See specification at page 3, lines 3-11, and page 20, lines 6-11.

Moreover, the criteria of Schneider does not recognize that mole fractions of gases within a microbubble accounts for the partial pressure and diffusion of gases in microbubble stabilization. Such diffusion provides gas to the bloodstream, and the present invention describes that partial pressure of the component gases and specifically states that partial pressure of the resulting gas mixture at 37°C must be above the equilibrium partial pressure of the osmotic agent.

In addition, Schneider discloses microvesicles that are liposomes and have hydrophilic interiors that have an aqueous environment. See Schneider at col. 4, lines 30-52. Some of Applicants microbubbles contain surfactant membranes and have hydrophobic interiors. Applicants note that skilled artisans would appreciate that Bunsen coefficients at room temperature are not the best criteria and gas solubility is raised as temperature is raised to the blood temperature (37°C).

Schneider does not mention or teach that an osmotically stabilized microbubble grows and shrinks in response to the gas saturation levels of the surrounding medium, a concept vital to the transport of physiological gases *in-vivo*. This expansion to take up physiological gases where they are plentiful, e.g. in the lung, and shrinking to deliver these gasses in low concentration regions, e.g. the tissues, provides the mechanism for enhanced gas transport. This growth and shrinkage, as required in the Applicants' claims, is the result of the microbubbles maintaining osmotic equilibrium. Schneider does not mention or suggest optimizing this vital property.

Thus, Applicants submit that Schneider does not suggest or disclose the presently amended claims and does not teach a result-effective variable to arrive at optimizing the claimed limitation of the mole ratios of the gases. Accordingly, Applicants respectfully request the withdrawal of this ground for rejection.

Rejection under 35 U.S.C. §103(a)

Claims 12, 19 have been rejected under 35 U.S.C. §103(a) over Schneider in view of U.S. Patent 4,265,251 (Tickner). Applicants respectfully traverse.

Schneider does not describe nor disclose the present invention as noted above.

Examiner acknowledges that Schneider does not teach oxygen. Applicants note that Schneider merely states that air in the microbubble is replaced by a physiologically acceptable gas and sets forth criteria as discussed above.

The Examiner also asserts that Tickner discloses use of oxygen in the contrast agents and maintains that gases such as oxygen, nitrogen, and Freons are substantially interchangeable and are functional equivalents. Thus, according to the Examiner, Tickner discloses a microbubble having only oxygen or nitrogen is functionally equivalent to a microbubble having a fluorocarbon.

Applicants submit that Tickner teaches that the preferred gas is carbon dioxide. As seen from the above Table, Freon's such as Freon 22 and Freon F-21 do not fit Schneider's criteria. Thus, Applicants fail to appreciate how gases such as oxygen, nitrogen and Freon are substantially interchangeable and functional equivalents as asserted by the Examiner. By contrast, the presently amended claims disclose perflurocarbons and fluorocarbons as gas osmotic agents with the partial pressure of the resulting modifier gas / osmotic agent gas mixture at 37°C greater than the equilibrium partial pressure of the osmotic agent when a modifier gas

such as oxygen diffuses through the bubble membrane. As stated above, neither Tickner nor Schneider teach or even mention the concept of microbubbles changing size due to osmotic equilibrium, a property vital to the enhanced transport of physiological gases, as required by the present claims.

Thus, Applicants contend that Tickner does not cure the deficiency of Schneider and provides no motivation to combine. Accordingly, Applicants respectfully request the withdrawal of this ground for rejection.

Rejection under 35 U.S.C. §103(a)

Claims 1-10, 12-20 have been rejected under 35 U.S.C. §103(a) over Schneider in view of U.S. Patent 5,536,753 (Clark). Applicants respectfully traverse.

Examiner acknowledges that Schneider does not teach oxygen and Applicants note that Schneider does not describe nor disclose the present invention as noted above.

The Examiner asserts that emulsions of Clark disclose oxygen transport. Applicants respectfully submit that the liquid emulsions discussed in Clark could not be used in combination with Schneider to obtain the microbubbles of the present invention.

Clark discloses perfluorocarbon emulsions composed of liquid droplets that transport oxygen based on the limited solubility of oxygen in perfluorocarbon liquids, which is somewhat higher that oxygen's solubility in water. The present invention is based on gas microbubbles that changing size due to osmotic equilibrium, a property vital to the enhanced transport of physiological gases, as required by the present claims. No liquid perfluorocarbon is present and the solubility of oxygen in liquid perfluorocarbons has no pertinence to the transport of gaseous oxygen inside gas microbubbles. The present invention is based on a completely different concept. The only mention of gaseous perfluorocarbons in Clark are in relation to the sometimes

fatal effects of gas emboli e.g. "gas embolism results which could lead to death in a short time", column 2, lines 3 to 4. Clark states that high vapor pressure fluorocarbons such as perfluorocyclohexanes, perfluorotrimethylcyclohexane and perfluoroisopropylcyclohexane cause emboli and must not be used and that perfluorocyclocarbons that have **lower vapor pressures** than perfluorocyclohexanes were considered critically necessary. See column 2, lines 1 to 7 and column 1, lines 50 to 59. The present invention preferably contains gas osmotic agents with **high vapor pressures**, "provided that they have sufficient vapor pressure, preferably at least about 50 or 100 Torr at body temperature, or more preferably at least about 150 or 200 Torr." See specification at page 20, lines 13-15. Thus Clark excludes, as possibly deadly, the perfluorocarbons that the present invention recommends. This is because the art of Clark, liquid emulsions, is very different from the gas microbubbles of the present invention.

Furthermore, Clark's emulsions require the liquid fluorocarbon to be dissolved in liquid hydrophobic oils e.g. triglycerides, whereas Applicants microbubbles do not. See for example, Clark at Claims 1 and 5. This is not an insubstantial difference. Applicants submit that liquid hydrophobic oils would affect the stability of the microbubbles and thus negatively impact the osmotic stabilization process in the presently amended claims.

Thus the Applicants contend that Clark does not cure the deficiency of Schneider and provides no motivation to combine. Accordingly, Applicants respectfully request the withdrawal of this grounds for rejection.

CONCLUSION

Applicants submit that all the claims are in condition for allowance and Applicants respectfully request that all claims be allowed.

Application Serial Number 09/991,445 Attorney Docket No. 48175-00005

Applicants request that any questions concerning this matter be directed to the undersigned at (609) 896-4584. If a telephone conference would be of assistance in advancing the prosecution of the present application, Applicants' undersigned attorney invites the Examiner to telephone at the number provided.

Applicants also authorizes the charge of any deficiency and/or the credit of any overpayment to deposit account 50-1943.

Respectfully submitted,

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